

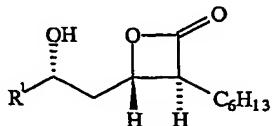
PROCESS FOR PREPARATION OF OXETAN-2-ONES

Field of the Invention

The present invention relates to a process for the preparation of diastereomerically and enantiomerically pure oxetan-2-ones. The present invention also relates to a process 5 for the preparation of ester derivatives of oxetan-2-ones.

Background of the Invention

Oxetan-2-ones of Formula I



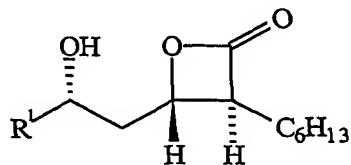
FORMULA I

wherein R¹ is undecyl or 2Z,5Z-undecadienyl have been reported. Such oxetan-2-ones are 10 useful intermediates for the preparation of lipstatin, tetrahydrolipstatin, esterastin, tetrahydroesterastin, and structurally related compounds, which are useful as pancreatic lipase-inhibiting agents, as well as for the prevention and treatment of obesity and hyperlipaemia.

Several processes have been reported for the preparation of oxetan-2-ones of 15 Formula I. For example in one synthesis, (3S,4S)-3-hexyl-4-(2S)-2-hydroxytridecyloxetan-2-one is prepared from tandem aldol-lactonization of (R)-3-(2-methoxyprop-2-oxy)tetradecanal and the lithium enolate of 1-octanoylbenzotriazole. However, such known processes require multiple steps, form unstable intermediates, or require complicated stereomeric purification processes, such as chromatography, and 20 therefore inevitably lead to poor yields or purity. As such, there remains a need for an improved process to synthesize oxetane-2-ones.

Summary of the Invention

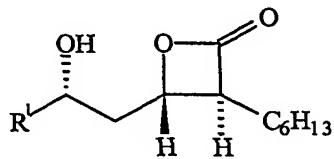
In accordance with one aspect of the invention, the invention encompasses a novel process for preparing an oxetan-2-one of Formula I,



FORMULA I

5 which provides improvements over prior methods of synthesis. Such oxetan-2-ones are useful as enzyme inhibitors.

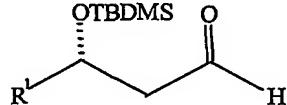
More particularly, there is provided a process for preparing an oxetan-2-one of Formula I,



FORMULA I

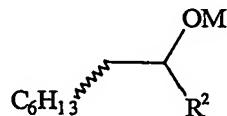
10 comprising the steps of:

reacting an aldehyde of Formula II



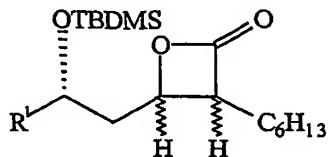
FORMULA II

with a metal enolate of Formula III



FORMULA III

to give a diastereomeric mixture of trans-oxetan-2-one of Formula IV



FORMULA IV (SSS+SRR)

hydrolyzing the diastereomeric mixture of trans-oxetan-2-one Formula IV to form the compound of Formula I; and

5 separating diastereomerically pure oxetan-2-ones of Formula I by crystallization, wherein R¹ can be undecyl or 2Z,5Z-undecadienyl and R² can be F, substituted or unsubstituted aryloxy, arylsulfanyl and heteroaryl, and M can be a monovalent metal, a divalent metal, a trivalent metal or a tetravalent metal.

In one aspect of the invention, R² is phenoxy or 1-benzotriazolyl and M is lithium, 10 MgBr, ZnCl or Ti(OR)₃ wherein R is alkyl. In another aspect of the invention, the reaction of the aldehyde of Formula II with the metal enolate of Formula III is performed in an inert organic solvent. The inert organic solvent can be diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane or tetrahydrofuran (THF).

In another aspect of the invention, the reaction of the aldehyde of Formula II with 15 the metal enolate of Formula III is carried out at a temperature of from about -120 °C to about -70 °C. In one particular embodiment, this reaction step is carried out at a temperature from about -100 °C to about -80 °C. The reaction of the aldehyde of Formula II with the metal enolate of Formula III can be quenched by addition of an acid or a salt solution and the compound of Formula IV can be recovered by extraction. In particular, 20 the acid can be hydrochloric acid and the salt solution can be ammonium chloride.

In another aspect of the invention, the hydrolysis of the diastereomeric trans-oxetan-2-one of Formula IV is carried out in the presence of an acidic catalyst and a polar solvent. In particular, the acidic catalyst can be an acid, a salt of a weak base, an acidic ion-exchange resin or acidic silica gel. The acid can be hydrofluoric acid or hydrochloric 25 acid and the salt of a weak base can be ammonium fluoride or pyridinium-4-toluenesulphonate. The polar solvent can be an alcohol, a cyclic ether, a nitrile, a dipolar aprotic solvent, an ester, or a mixture thereof; the alcohol can be methanol, ethanol or

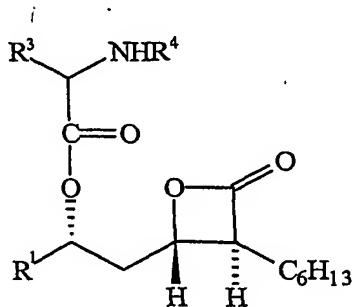
isopropanol; the cyclic ether can be dioxane or tetrahydrofuran (THF); the nitrile can be acetonitrile; the dipolar aprotic solvent can be dimethylformamide, dimethyl sulfoxide, sulfolane or N-methylpyrrolidone; and the ester can be ethyl acetate, or isopropyl acetate.

In one aspect of the invention, the hydrolysis of the compound of Formula IV is
5 carried out at a temperature from about -20 °C to about 120 °C. In one particular embodiment, the temperature is from about 0 °C to about 60 °C.

In another aspect of the invention, the diastereomerically pure oxetan-2-ones of
10 Formula I are separated by crystallization from an aliphatic hydrocarbon solvent. The aliphatic hydrocarbon solvent can be hexane, pentane, heptane, cyclohexane, or mixtures thereof.

In yet another aspect of the invention, the diastereomerically pure oxetan-2-ones of
15 Formula I are separated by crystallization from a mixture of an aliphatic hydrocarbon solvent along with at least one of an aromatic hydrocarbon, an ether, a chlorinated hydrocarbon, an ester, a ketone. In particular, the aromatic hydrocarbon can be toluene or xylene; the ether can be diisopropyl ether, dibutyl ether, diethyl ether, methyl tert-butyl ether, dioxane or tetrahydrofuran; the chlorinated hydrocarbon can be methylenedichloride or ethylenedichloride; the ester can be ethyl acetate or isopropyl acetate; and the ketone can be acetone or methylisobutylketone.

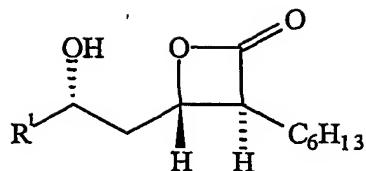
The present invention also encompasses a process for preparing a compound of
20 Formula V



FORMULA V

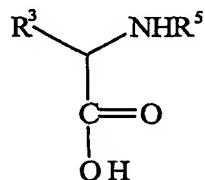
comprising the steps of:

treating an oxetan-2-one of Formula I



FORMULA I

with an acid or acid anhydride of Formula VI



FORMULA VI

or a mixed anhydride thereof, and dicyclohexylcarbodiimide;

5 cleaving off R⁵; and

reacting with an alkanoylating agent having an R⁴ group to introduce the group R⁴,
wherein R¹ undecyl or 2Z,5Z-undecadienyl, R³ can be isobutyl or carbamoylmethyl, R⁴ can be formyl or acetyl, and R⁵ can be an amino protecting group.

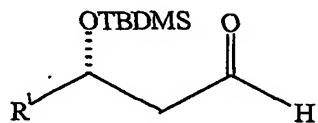
10 In one aspect of the invention, R⁵ can be benzyloxycarbonyl or p-nitrobenzyloxycarbonyl. In another aspect of the invention, the alkanoylating agent can be an acid anhydride of R⁴-COOH or R⁴X wherein X is a halide. Particular alkanoylating agents include formic acid anhydride, acetic anhydride, formyl halide or acetyl halide.

15 In one aspect of the invention, the treatment of oxetan-2-one of Formula I with the acid of Formula VI is performed in a solvent, where the solvent can be a hydrocarbon, a chlorinated hydrocarbon, an ether, an ester, a dipolar aprotic solvent, or mixtures thereof. In particular, the hydrocarbon can be hexane, cyclohexane, toluene, or xylene; the chlorinated hydrocarbon can be methylenedichloride or ethylenedichloride; the ether can be diethyl ether, methyl tert-butyl ether, dioxane or tetrahydrofuran; the ester can be ethyl acetate or isopropyl acetate; and the dipolar aprotic solvent can be dimethylformamide or 20 dimethylacetamide.

In one aspect of the invention, the treatment of oxetan-2-one of Formula I with the acid of Formula VI is performed in the presence of dimethylaminopyridine. In another aspect of the invention, the treatment of oxetan-2-one of Formula I with the acid of Formula VI is performed at a temperature from about -20°C to about 40°C. In yet another aspect of the invention, R⁵ is cleaved by hydrogenation in the presence of a hydrogenation catalyst and a solvent at a temperature from about 10 to about 75 °C.

In another aspect of the invention, the invention encompasses a compound prepared by a process comprising the steps of:

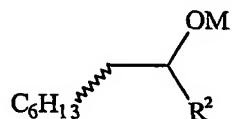
a. reacting an aldehyde of Formula II



FORMULA II

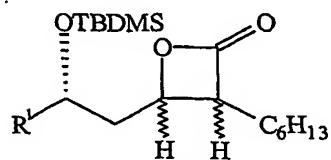
10

with a metal enolate of Formula III



FORMULA III

to give a diastereomeric mixture of trans-oxetan-2-one of Formula IV



FORMULA IV (SSS+SRR)

15 b. hydrolyzing the diastereomeric mixture of trans-oxetan-2-one of Formula IV to form the compound of Formula I; and

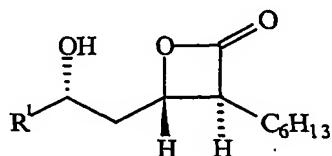
c. separating of diastereomerically pure oxetan-2-ones of Formula I by crystallization,

wherein R¹ is undecyl or 2Z,5Z-undecadienyl and R² is selected from the group consisting of F, substituted or unsubstituted aryloxy, arylsulfanyl and heteroaryl, and M is selected from the group consisting of a monovalent metal, a divalent metal, a trivalent metal and a tetravalent metal.

5

Detailed Description of the Invention

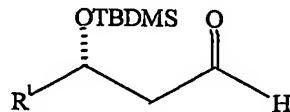
The present invention generally is directed a process for preparing oxetan-2-one of Formula I



FORMULA I

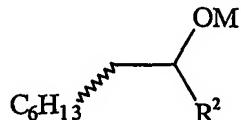
comprising the steps of:

10 a. reacting an aldehyde of Formula II



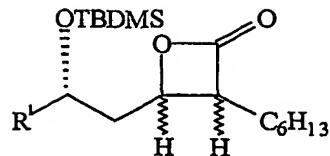
FORMULA II

b. wherein with a metal enolate of Formula III



FORMULA III

to give a diastereomeric mixture of trans-oxetan-2-one of Formula IV

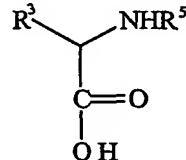


FORMULA IV (SSS+SRR)

- c. hydrolyzing the resulting diastereomeric mixture of trans-oxetan-2-ones of Formula IV; and
- d. separating the diastereomerically pure oxetan-2-ones of Formula I by 5 crystallization,

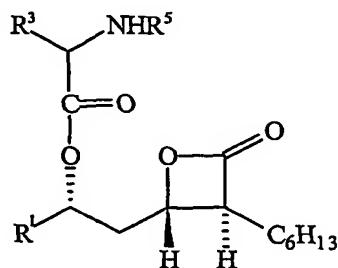
wherein R¹ can be undecyl or 2Z, 5Z-undecadienyl; R² can be fluorine, substituted or unsubstituted aryloxy, arylsulfanyl, and heteroaryl groups; M can be mono-, di-, tri-, and tetravalent metal containing groups.

In another aspect, a process for preparing a compound of Formula V is provided, 10 which comprises treating the oxetan-2-one of Formula I directly with an acid of Formula VI



FORMULA VI

and dicyclohexylcarbodiimide, wherein R⁵ can be an amino protecting group and R³ can be isobutyl or carbamoylmethyl; followed by cleaving off the amino protecting group R⁵ 15 of the obtained ester of Formula VIII



FORMULA VIII

wherein R¹ can be undecyl or 2Z, 5Z-undecadienyl; and reacting the compound of Formula VIII with an alkanoylating agent containing an R⁴ group to introduce R⁴ to obtain the compound of Formula V.

5 The aryl part of the aryloxy and arylsulfonyl groups, as used herein, includes any aromatic mono- or polycyclic ring system, such as benzene, and naphthalene. The heteroaryl group includes mono- or polycyclic heteroaromatic ring systems, such as pyridine and furan.

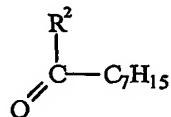
10 Examples of R² include phenoxy or 1-benzotriazolyl. Examples of M include Li, MgBr, ZnCl and Ti(OR)₃, wherein R is alkyl.

15 The reaction of the aldehyde of Formula II with the metal enolate of Formula III may be performed in a suitable solvent. Suitable solvents for the reaction are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include ethers, such as diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF).

20 In general, the reaction may be carried out at a temperature range from about -120°C to about -70°C, including, for example, at a temperature range from about -100°C to about -80°C.

25 The reaction can be quenched by an acid, such as hydrochloric acid, or a salt solution, such as ammonium chloride solution and the diastereomeric mixture (SSS and SRR) of trans-oxetan-2-ones of Formula IV can be recovered by extraction followed by crystallization.

Lithium enolates of the Formula III (M=Li) may be prepared from the activated carboxylic acid derivative of Formula IX



FORMULA IX

25 wherein R² can be phenoxy or 1-benzotriazolyl, by adding the activated carboxylic acid derivative of Formula IX to a solution of a strong base, such as lithium diisopropylamide or lithium hexamethyldisilazide, at an appropriate temperature, for example at about

-70 °C. Other metal enolates of Formula III may be prepared from the corresponding lithium enolate by addition of metal salts, such as MgBr₂, ZnCl₂ or Ti(OPr)₃Cl.

Aldehyde of Formula II may be prepared by methods known in the art, such as those described in *Synthesis*, 1994, 1294-1300 for the corresponding R enantiomer, using

5 (S)- BINAP instead of (R)- BINAP for the asymmetric catalytic hydrogenation.

The hydrolysis of the diastereomeric trans-oxetan-2-one of Formula IV to remove the tert-butyldimethylsilyl protecting group may be carried out in the presence of an acidic catalyst in a polar solvent to afford an oxetan-2-one of the Formula I (SSS) and the other trans-diastereomer (SRR).

10 Examples of acidic catalyst include an acid, such as hydrofluoric acid and hydrochloric acid; a salt of a weak base, such as ammonium fluoride and pyridinium-4-toluenesulphonate; an acidic ion-exchange resin, such as Dowex 20[®] (E. Merck), or acidic silica gel (obtained by treatment of silica gel with methanolic hydrochloric acid).

15 Examples of polar solvents include alcohols, such as methanol, ethanol and isopropanol; cyclic ethers, such as dioxane and tetrahydrofuran (THF); nitriles, such as acetonitrile; dipolar aprotic solvents, such as dimethylformamide, dimethyl sulfoxide, sulfolane and N-methylpyrrolidone; esters, such as ethyl acetate and isopropyl acetate; and mixtures thereof.

20 The hydrolysis may be carried out at a temperature range from about -20 °C to about 120 °C, at a temperature range from about 0 °C to about 60 °C, or even at a temperature range from about 10 °C to about 40 °C.

25 The diastereomerically pure oxetan-2-one of the Formula I is obtained from the diastereomeric mixture by crystallization from a suitable solvent(s). Examples of suitable solvents include aliphatic hydrocarbons, such as hexane, pentane, heptane, cyclohexane, and mixtures thereof. Aliphatic hydrocarbons can be used in a mixture with other solvents, including aromatic hydrocarbons, such as toluene, and xylene; ethers, such as diisopropyl ether, dibutyl ether, diethyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF); chlorinated hydrocarbons, such as methylenedichloride and ethylenedichloride; esters, such as ethyl acetate and isopropyl acetate; ketones, such as 30 acetone and methylisobutylketone (MIBK); and any combinations thereof.

The oxetan-2-one of Formula I may be converted to a compound of Formula V, by methods known in the art, such as those described in U.S. Patent No. 4,983,746 and U.S.

Patent No. 5,175,186, which are incorporated herein by reference; as well as in *Helv. Chim. Acta*, 1987, 70, 1412-1418; and *J. Org. Chem.* 1988, 53, 1218-1221.

In general, the acid anhydride of an acid of Formula VI, or a mixed anhydride thereof, is used for esterification of the oxetan-2-one of Formula I; followed by cleaving 5 off the amino protecting group R^5 of the ester of Formula VIII so obtained; and reacting with an alkanoylating agent, which introduces the group R^4 to obtain the compound of Formula V.

Alternatively, the compound of Formula V can be prepared by directly esterifying the oxetan-2-one of Formula I with an acid anhydride of an acid of Formula VII, or a 10 mixed anhydride thereof, wherein R^3 and R^4 are as defined in Formula V. However, lower yields may be obtained with this process (*J. Org. Chem.* 1991, 56, 4716; *Chem. Comm.* 1999, 17, 1743-1744).

The compounds of Formula V, wherein R^1 is undecyl, may also be prepared by 15 hydrogenating a compound of Formula V, wherein R^1 is 2Z,5Z-undecadienyl.

Examples of amino protecting group R^5 include benzyloxycarbonyl and p-nitrobenzyloxycarbonyl.

The acid anhydrides may be obtained by reacting an acid of Formula VI or 20 Formula VII, with dicyclohexylcarbodiimide or N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide. The preparation of this acid anhydride may be carried out in a suitable solvent such as methylene chloride while cooling, for example to a temperature from about 0 °C to about 5 °C. The dicyclohexylurea byproduct is filtered off and the subsequent esterification can be carried out in a solvent such as dimethylformamide in the presence of dimethylaminopyridine at room temperature.

The mixed acid anhydride may be obtained by reacting an acid of Formula VI or 25 Formula VII, with a suitable acid halide (such as pivaloyl chloride) in a solvent (such as dimethylformamide) while cooling, for example to a temperature from about -5 °C to about 0 °C, and the subsequent esterification can be carried out in the same solvent at the same temperature.

The cleavage of amino protecting group R^5 may be carried out by hydrogenation in 30 a solvent, for example, ethers, such as dioxane and tetrahydrofuran; chlorinated hydrocarbons, such as methylenedichloride and ethylenedichloride; and esters, such as ethyl acetate and isopropyl acetate in the presence of a hydrogenation catalyst, such as

palladium-on-carbon, at a temperature of about 10 °C to about 75 °C. The hydrogenation may be carried out at normal pressure, or at elevated pressure. In general, it may be carried out at a hydrogen pressure range from 1 to 2 atmospheres.

In one aspect, an undecadienyl group present in Formula V can be hydrogenated to 5 the undecyl group during the hydrogenolytic cleavage of the amino protecting group.

The alkanoylating agent may be an acid anhydride, such as formic acid anhydride or acetic acid anhydride; a mixed acid anhydride, such as formic acid/acetic acid anhydride; or an acid halide, such as acetyl chloride. The alkanylation may be carried out in a suitable solvent, for example, ethers, such as dioxane and tetrahydrofuran, and 10 chlorinated hydrocarbons, such as methylenedichloride and ethylenedichloride, at room temperature. A base, such as triethylamine, may be added in cases where an acid halide is used.

An improved process for preparing a compound of Formula V is provided, which involves treating the oxetan-2-one of Formula I directly with an acid of Formula VI, and 15 dicyclohexylcarbodiimide, followed by deprotection of the amino protecting group and alkanylation as above.

The ester of Formula VIII is thus obtained in a single step, wherein the acid anhydride of Formula VI is formed *in situ* and simultaneously used up in esterification. The process may be performed in a suitable solvent, optionally in the presence of 20 dimethylaminopyridine. Examples of suitable solvents include chlorinated hydrocarbons, such as methylenedichloride and ethylenedichloride; hydrocarbons, such as hexane, cyclohexane, toluene, and xylene; ethers, such as diethyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF); dipolar aprotic solvents, such as dimethylformamide and dimethylacetamide; esters, such as ethyl acetate and isopropyl acetate; and mixtures 25 thereof. The reaction may be carried out at a temperature range from about -20 °C to about 40 °C.

The present invention also is directed to a compound prepared by the processes described herein.

Examples

In the following section preferred embodiments are described by way of examples to illustrate the process. However, these are not intended in any way to limit the scope of the claims. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Example 1. Preparation of methyl (S)-3-(tert-butyldimethylsiloxy) tetradecanoate

A solution of methyl (S)-3-hydroxytetra deaconate (100 g, 0.387 mol) was added to dimethylformamide (150 mL), cooled to 5 °C to 10 °C, and imidazole (66.2 g, 0.972 mL) in dimethylformamide (150 mL) was added, followed by the drop-wise addition of 10 tert-butyldimethylsilyl chloride (87.0 g, 0.577 mol) in dimethylformamide (150mL). The mixture was then stirred for 8 to 10 hours at room temperature. The mixture was poured into water (5.0 L) with stirring and the product extracted into hexane (3 x 1.0 L). The combined organic layer was washed with saturated sodium chloride solution followed by water, dried and concentrated under reduced pressure to obtain the title compound as a 15 residue (156 g).

Example 2. Preparation of (S)-3-(tert-butyldimethylsiloxy) tetradecanal

A solution of methyl-(S)-3-(tert-butyldimethylsiloxy) tetradecanoate (155 g) in toluene (600 mL) was cooled to -80 °C. A solution of DIBAL-H (20% in toluene, 400 mL) was diluted with another 400 mL of toluene and added drop-wise at -80 °C during 2 20 to 3 hours under stirring. The mixture was stirred at -80 °C for 30 minutes. Methanol (50 mL) was added to the reaction at -70 °C to -80 °C. Further, saturated sodium chloride solution (400 mL) was added followed by HYFLOW (50 g) and sodium sulfate (25 g) at room temperature. The solid was filtered and washed with toluene (200 mL). The combined organic layer was washed with saturated sodium chloride solution (200 mL) 25 followed by water (200 mL), dried over sodium sulfate, concentrate under reduced pressure to obtain the title compound as a residue (136 g).

Example 3. Preparation of 3-hexyl-4[(2s)-2-tert-butyldimethylsiloxytridecyl] oxetan-2-one [(3S,4S) + (3R,4R)]

Lithium hexamethyldisilazide (20% THF, 400 mL) was cooled to -95 °C and a 30 solution of N-octanoylbenzotriazole (100 g in 350 mL THF) pre-cooled to -40 °C was added at a rate sufficient to maintain the temperature at -95 °C. After complete addition, the reaction mixture was stirred at -95°C for 30 minutes. The crude (S)-3-(tert-butyl

dimethylsiloxy)tetradecanal prepared in Example 2 above (135 g in 200 mL THF) was cooled to -50°C and then added to the lithium enolate at a rate sufficient to maintain the temperature at -95 °C for 30 minutes and then warmed to 0 °C. Dilute hydrochloric acid (2N, 380 mL) was then added and the mixture stirred for 10 to 15 minutes. Hexane (500 mL) was then added, stirred for 15 minutes and the organic layer was separated. Aqueous layer was re-extracted with hexane (300 mL). The combined hexane layer was washed with saturated sodium chloride solution (200 mL) followed by water (200 mL) and concentrated under reduce pressure until a thick mass was obtained. Fresh hexane (600 mL) was added to the thick mass and stirred at room temperature for 1 hour. The solid that precipitated out (benzotriazole) was filtered off and washed with hexane. The combined hexane layer was concentrated under reduce pressure to get a thick residue, which was dissolved in ethylacetate:hexane (5:95 v/v) and passed through silica gel bed to get the title diastereomeric mixture (150 g).

Example 4. Preparation of (3S,4S)-3-hexyl-4[(2S)-2-hydroxy]oxetan-2-one

15 A solution of the diastereomeric oxetanone mixture obtained in Example 3 (150 g) in acetonitrile (600 mL) was cooled to 10 °C to 15 °C. Aqueous hydrofluoric acid (40%, 15 mL) was added drop-wise and the reaction mixture was stirred for 10 hours at room temperature. The mixture was poured in water (3 L) and extracted with hexane (750 mL). The hexane layer was separated and the aqueous layer was re-extracted with hexane (250 mL). The hexane layers were combined and washed with saturated sodium bicarbonate solution (300 mL), followed by washing with water. Hexane was distilled out under reduce pressure to obtain a thick residue (130 g), which was then stirred in hexane (450 mL) at 0 °C. The precipitated solid was filtered and washed with cold hexane to get 58 g of the title compound.

25 Example 5. Preparation of (S)-N-[(benzyloxy)carbonyl]leucine (S)-1-[[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]dodecyl ester

A solution of (S)-N-[(benzyloxy)carbonyl]leucine (200 g, 0.6214 mol) in toluene (100 mL), was cooled to about -10 °C to about 0 °C. 1,3-Dicyclohexylcarbodiimide (90 g, 0.436 mol) in toluene (300 mL) was slowly added to the solution, followed by the addition 30 of the product from Example 4 (100 g, 0.282 mol) and 4-(N, N-dimethylamino)pyridine (10 g). The reaction mixture was stirred for 1 hour at 0 °C to 10 °C, the residual urea derivative was filtered off, and the filter cake was washed with toluene (100 mL). The

toluene filtrate was combined washed with aqueous hydrochloric acid, sodium bicarbonate and water. After carbon treatment of toluene layer and recovery of toluene, the product was recrystallized with hexane (100 mL), filtered, washed with hexane (200 mL) and dried to provide 150 g (yield: 89%) of the title compound.

5 Example 6. Preparation of (S)-leucine (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester

A solution of the product from Example 5 (100 g, 0.166 mol) in methanol (300 mL) was hydrogenated in the presence of 10% Pd/C (10 g, 50% moisture) at room temperature under hydrogen atmosphere (20 to 60 psi) for 2 hours. The title product was 10 obtained after filtration and evaporation of methanol as a residual oil 80 g (purity: 90% by HPLC, yield: 93%).

Example 7. Preparation of (S)-N-formylleucine (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]dodecyl ester (Orlistat)

To the solution of the product from Example 6 (100 g, 0.214 mol) in 15 dichloromethane (700 mL), formic acid/acetic anhydride reagent (245g, obtained by mixing 157.6 g of formic acid in 87.4 g of acetic anhydride) was added slowly at about -5 °C to about 5 °C. The reaction was monitored by TLC (ethylacetate:hexane at 30:70 v/v, I₂). After completion of the reaction the reaction mixture was washed with water, sodium bicarbonate solution and brine, the dichloromethane was recovered completely. 20 Orlistat (63.0 g) was obtained after recrystallization with n-pentane.

Assay: 99.4% by HPLC